See related commentary on pg 2339

HLA-C*06:02 Allele and Response to IL-12/23 Inhibition: Results from the Ustekinumab Phase 3 Psoriasis Program

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Several small studies suggest that the presence of the human leukocyte antigen (HLA)-Cw6 (C*06:02) allele may be a predictor of improved response to ustekinumab. This study was designed to assess the association of the HLA-C*06:02 allele with response to ustekinumab in large cohorts of patients from the phase 3 studies of ustekinumab in moderate-to-severe psoriasis. In this retrospective study, both HLA-C*06:02-positive and -negative patients demonstrated good responses to ustekinumab (86% vs. 76%, respectively, achieved at least a 75% improvement from baseline in Psoriasis Area and Severity Index [PASI 75] at week 24). A modestly higher proportion of HLA-C*06:02-positive than HLA-C*06:02-negative patients achieved PASI 75/90 responses at weeks 12 and 24. The largest response difference between the positive and negative patients (17.9%) was observed for PASI 75 (week 12), with smaller differences noted at later time points for PASI 90 (11.8% at week 24) and PASI 100 (10.2% at week 28). A differential response to ustekinumab has been confirmed in HLA-C*06:02-positive versus HLA-C*06:02-negative patients; however, this difference is modest, particularly at the higher response rate thresholds (PASI 90/100) and later time points (weeks 24/28).

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INTRODUCTION

Psoriasis is a chronic immune-mediated skin disease that is estimated to affect 2–4% of the population in Western countries, with a higher prevalence in the United States, Canada, and Europe compared with other countries (Christophers, 2001; Gelfand et al., 2005; Kurd and Gelfand, 2008; Parisi et al., 2013). Variability in the prevalence of psoriasis is due to numerous factors including age, gender, geography, and ethnicity (Parisi et al., 2013). Psoriasis is a multifactorial disorder in which complex interactions between immune pathways, environmental factors, and genetics play a role in its etiology (Nestle et al., 2009); in fact, there is strong evidence through genetic epidemiologic studies that the disease is 60–90% heritable, which is the greatest reported for multigenic diseases (Elder et al., 1994). The concordance rate for psoriasis in monozygotic twins ranges from approximately 35%–73% compared with 6%–20% in dizygotic twins (Brandrup et al., 1978; Duffy et al., 1993; Farber et al., 1974; Grjibovski et al., 2007; Lonnberg et al., 2013). Although greater than 40 psoriasis susceptibility loci have been identified to date (Nair et al., 2009; Strange et al., 2010; Sun et al., 2010; Tsoi et al., 2015), the PSORS1 genetic locus, a 220-kb region found on chromosome 6p21 (Veal et al., 2002), is associated with the greatest risk for psoriasis, conferring 35–50% of heritability (Basko-Plluska and Petronic-Rosic, 2012). Within the PSORS1 region, human leukocyte antigen (HLA)-Cw6 has been identified as the strongest psoriasis susceptibility allele (Capon et al., 2002; Gudjonsson et al., 2003; Nair et al., 2006; Zhang et al., 2003).

The HLA-C*06:02 allele is present in 47–64% of patients with psoriasis and increases the risk of disease by 9- to 23-fold (Feng et al., 2009; Gudjonsson et al. 2003; Okada et al., 2014; Tiilikainen et al., 1980). The presence of HLA-C*06:02 is reported to be associated with an earlier onset of psoriasis, a more severe disease course, and a greater prevalence of the guttate phenotype (Gudjonsson et al., 2003, 2006; Mallon et al., 2000). Although the precise mechanism by which HLA-C*06:02 contributes to disease etiology is still unclear, HLA-C*06:02 encodes a major histocompatibility complex class I molecule that may be involved in presentation of autoantigens to CD8+ T cells that clonally expand in psoriasis lesions (Arakawa et al., 2015). A disintegrin-like and metalloprotease domain containing thrombospondin type 1 motif-like 5 has recently been identified as an HLA-C*06:02-restricted melanocyte-derived autoantigen that can drive skin-specific psoriatic immune activation (Arakawa et al., 2015).

At the population level, a significant percentage of patients with psoriasis do not have the HLA-C*06:02 allele (Tiilikainen et al., 1980), supporting the assertion that psoriasis is a multigenic disease in which additional genes may contribute to susceptibility, including immune-related genes such as *IL-12B*, *IL-23A*, *IL-23R*, *TNFAIP3* and *ERAP1* (Eiris et al., 2014; Harden et al., 2015; Strange et al., 2010;

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Abbreviations: HLA, human leukocyte antigen; HLA-C*06:02-POS, HLA-C*06:02-positive; HLA-C*06:02-NEG, HLA-C*06:02-negative; PASI, Psoriasis Area and Severity Index; PASI 50/75/70, 50/75/90% improvement from baseline in Psoriasis Area and Severity Index; TNF, tumor necrosis factor

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Tejasvi et al., 2012). Because of the genetic complexity of psoriasis, there is significant variability in the clinical presentation of the disease (Griffiths et al., 2007). Likewise, different types of psoriasis do not always respond to the same treatment, and even within the same type of disease, there are responders and nonresponders to each treatment (Talamonti et al., 2013). Although biological agents have significantly contributed to advancements in the clinical management of psoriasis, use of these treatments is associated with varying degrees of efficacy, safety, risk, and cost. As a result, the identification of pharmacogenetic biomarkers that could improve treatment outcomes and/or minimize significant side effects is desirable. However, little is known about the link between pharmacogenetics and biological therapies in psoriasis (Ryan et al., 2011). Patients with psoriasis positive for HLA-C*06:02 have been suggested to have significantly higher response rates to efalizumab (anti-CD11a) (Gulliver, 2009). The association between HLA-C*06:02 and response to tumor necrosis factor (TNF) inhibitors is not well understood; however, it has been reported that patients expressing two single nucleotide polymorphisms in the gene encoding *TNFAIP3* have good responses to TNF therapies (Tejasvi et al., 2012). To date, although these markers have been suggested to be associated with response, no genetic markers have been confirmed to be associated with response to biological therapies in large well-defined cohorts of patients with psoriasis.

Ustekinumab is a fully human monoclonal antibody that targets the common p40 subunit of the IL-12 and IL-23 cytokines. Multiple clinical trials have demonstrated the clinical utility of ustekinumab in the treatment of moderate-to-severe psoriasis (Griffiths et al., 2010; Leonardi et al., 2008; Papp et al., 2008) and psoriatic arthritis (McInnes et al., 2013; Ritchlin et al., 2014). It was recently reported in a small cohort of 51 patients with psoriasis that the HLA-C*06:02 allele was associated with a rapid and beneficial clinical response to ustekinumab (Talamonti et al., 2013, 2016). In the current study, we report the results from a retrospective study conducted to evaluate the role of HLA-C*06:02 and the response to ustekinumab in a large cohort of patients with psoriasis (n = 601) who originally participated in the phase 3 clinical trials PHOENIX 1 (Leonardi et al., 2008), PHOENIX 2 (Papp et al., 2008), and ACCEPT (Griffiths et al., 2010).

RESULTS

The prevalence of the HLA-C*06:02 genotype in this study consisting of patients with moderate-to-severe plaque psoriasis from the PHOENIX 1, PHOENIX 2, and ACCEPT randomized, controlled clinical studies was 44.6% (Supplementary Table S1 online). Patient baseline demographics and disease characteristics were similar across the three studies. Across studies, similar proportions of patients achieved a Psoriasis Area and Severity Index (PASI) 75 response at week 12 (the primary endpoint for each study). HLA-C*06:02-positive (POS) in the combined population was associated with longer disease duration, an earlier age of onset, and with modestly lower baseline PASI scores compared with patients who were HLA-C*06:02-negative (NEG) (Table 1). There were no significant associations of HLA-C*06:02 with other disease characteristics such as scalp psoriasis (data not shown).

The association of HLA-C*06:02 and clinical response to ustekinumab was assessed measuring 50/75/90/100% improvement from baseline in PASI (PASI 50, PASI 75, PASI 90, and PASI 100) (Figure 1) and physician global assessment responses (Supplementary Figure S1 online). Because similar results were observed in patients who received ustekinumab 45 or 90 mg treatment (data not shown), the two dose groups were combined in this analysis to yield a larger sample size. A higher percentage of HLA-C*06:02-POS patients achieved PASI 50, 75, 90, and 100 responses at weeks 4, 12, 24, and 28 compared with HLA-C*06:02-NEG patients (Figure 1). However, the difference was modest, reaching significance for PASI 50 responses at weeks 4 (Figure 1a), as well as PASI 75 responses at weeks 4 and 12 (Figure 1b). The difference in PASI responses between HLA-C*06:02-POS and HLA-C*06:02-NEG patients ranged from 0−17.9%, whereas the difference between the overall population (i.e., regardless of genotype) and the HLA-C*06:02-POS population ranged from 0−10.4% (Figure 1). The largest response difference between the POS and NEG patients (17.9%) or the overall population (10.4%) was observed for PASI 75 at week 12. Similarly, a greater proportion of HLA-C*06:02-POS patients achieved a physician global assessment score of 0 or 1 (cleared or minimal) than HLA-C*06:02-NEG patients (Figure S1 online), only reaching significance at week 4 with a difference of 15% between HLA-C*06:02-POS and HLA-C*06:02-NEG patients.

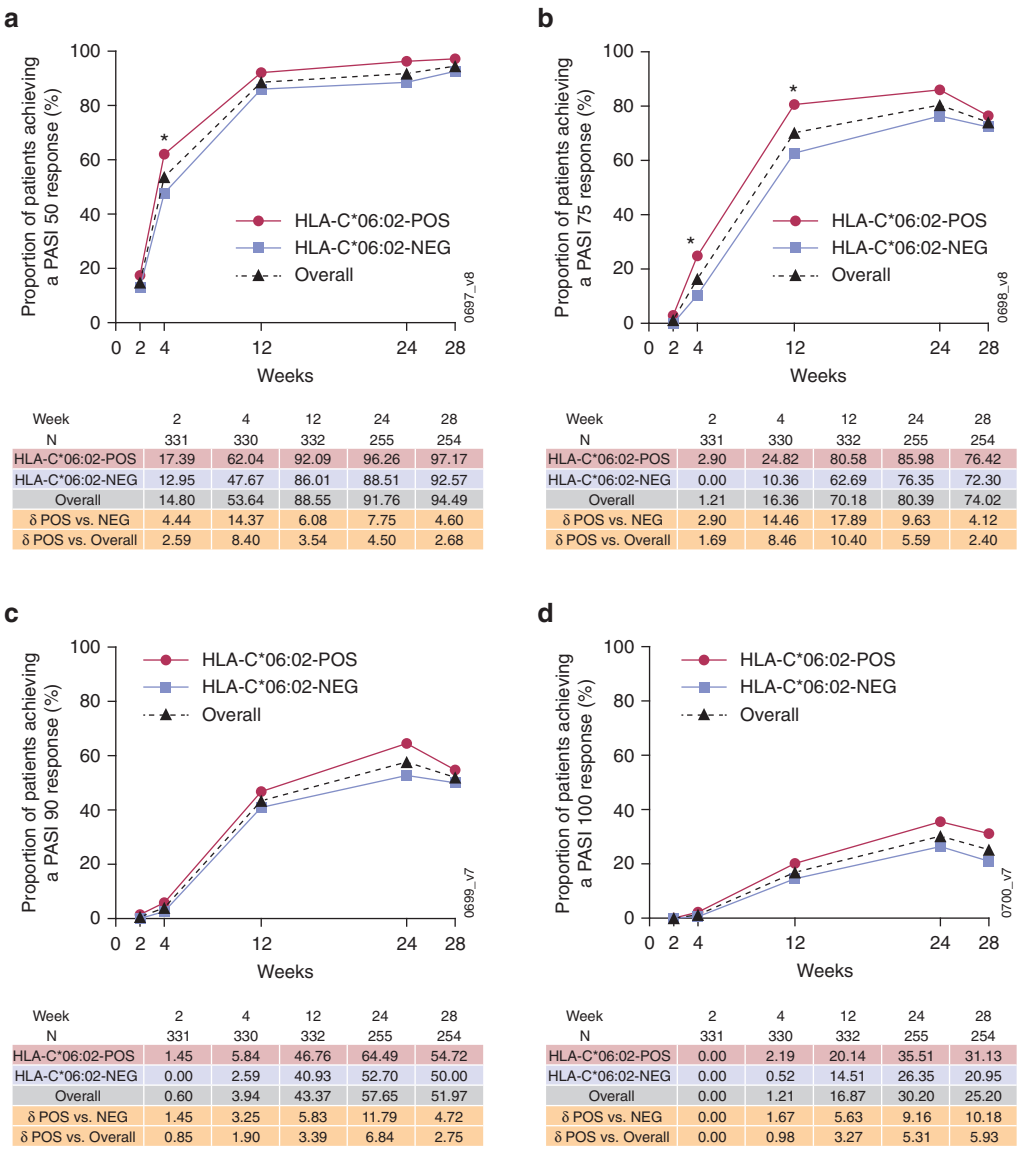
When patients were stratified by the recommended weight-based dosing paradigm (ustekinumab 45 mg for patients <100 kg; ustekinumab 90 mg for patients ≥100 kg), the differences in PASI 75 response by HLA-C*06:02 were slightly magnified, especially in the ≥100 kg subpopulation with a range of 0−15.9% when compared with the overall population and the HLA-C*06:02-POS patients (Figure 2). Patients were also stratified by prior treatment with anti-TNF agents. The largest response differences between HLA-C*06:02-POS patients and the overall population observed in anti-TNF-naïve and anti-TNF-experienced patients were 10.8% at week 4 and 6.7% at week 24, respectively (Figure 3), demonstrating that HLA-C*06:02 status did not differentially influence PASI 75 response based on prior anti-TNF exposure.

Table 1. Psoriasis characteristics in patients across three studies by HLA-C*06:02 status

	HLA-C*06:02-POS patients (N = 233)	HLA-C*06:02-NEG patients (N = 290)	*P*-value
Age of psoriasis onset, y	21.4 ± 11.0	27.7 ± 13.6	<0.0001
Disease duration, y	24.2 ± 12.9	20.3 ± 11.1	0.0003
Baseline PASI score	18.1 ± 6.5	19.4 ± 6.6	0.0275

Values are reported as mean ± SD, unless otherwise noted. *P*-values are based on the analysis of variance.

Abbreviations: HLA, human leukocyte antigen; HLA-C*06:02-POS, HLA-C*06:02-positive; HLA-C*06:02-NEG, HLA-C*06:02-negative; PASI, Psoriasis Area and Severity Index.



Week	2	4	12	24	28
N	331	330	332	255	254
HLA-C*06:02-POS	17.39	62.04	92.09	96.26	97.17
HLA-C*06:02-NEG	12.95	47.67	86.01	88.51	92.57
Overall	14.80	53.64	88.55	91.76	94.49
δ POS vs. NEG	4.44	14.37	6.08	7.75	4.60
δ POS vs. Overall	2.59	8.40	3.54	4.50	2.68

Week	2	4	12	24	28
N	331	330	332	255	254
HLA-C*06:02-POS	2.90	24.82	80.58	85.98	76.42
HLA-C*06:02-NEG	0.00	10.36	62.69	76.35	72.30
Overall	1.21	16.36	70.18	80.39	74.02
δ POS vs. NEG	2.90	14.46	17.89	9.63	4.12
δ POS vs. Overall	1.69	8.46	10.40	5.59	2.40

Week	2	4	12	24	28
N	331	330	332	255	254
HLA-C*06:02-POS	1.45	5.84	46.76	64.49	54.72
HLA-C*06:02-NEG	0.00	2.59	40.93	52.70	50.00
Overall	0.60	3.94	43.37	57.65	51.97
δ POS vs. NEG	1.45	3.25	5.83	11.79	4.72
δ POS vs. Overall	0.85	1.90	3.39	6.84	2.75

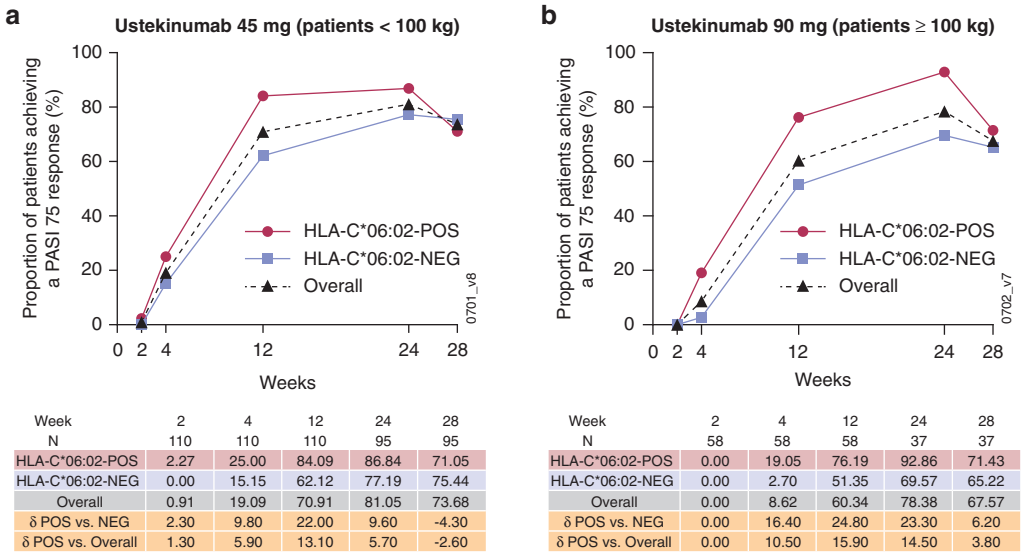
Week	2	4	12	24	28
N	331	330	332	255	254
HLA-C*06:02-POS	0.00	2.19	20.14	35.51	31.13
HLA-C*06:02-NEG	0.00	0.52	14.51	26.35	20.95
Overall	0.00	1.21	16.87	30.20	25.20
δ POS vs. NEG	0.00	1.67	5.63	9.16	10.18
δ POS vs. Overall	0.00	0.98	3.27	5.31	5.93

Figure 1. Psoriasis Area and Severity Index (PASI) response by human leukocyte antigen (HLA)-C*06:02 status. The proportion of HLA-C*06:02-positive (POS) and -negative (NEG) patients achieving a (**a**) 50% improvement in PASI from baseline (PASI 50); (**b**) PASI 75 response; (**c**) PASI 90 response; (**d**) PASI 100 response following ustekinumab treatment (45 and 90 mg dose groups combined). *$P < 0.05$ based on adjusted Fisher's exact test; δ, difference between values.

The association of HLA-C*06:02 and long-term efficacy was also assessed in the long-term extension of the PHOENIX 1 and PHOENIX 2 studies. The PHOENIX 1 study population was used to assess efficacy rates by HLA-C*06:02 status in patients at their 5-year final efficacy assessment (Table 2). In general, HLA-C*06:02-POS patients had modestly higher efficacy rates than HLA-C*06:02-NEG patients, with statistical significance for PASI 50 (92.8% HLA-C*06:02-POS vs. 80.5% HLA-C*06:02-NEG) and PASI 75 (82.6% HLA-C*06:02-POS vs. 64.4% HLA-C*06:02-NEG) response rates. The PHOENIX 2 study evaluated dosing adjustment either by dose (ustekinumab 45 to 90 mg), or by dose interval (every 12 weeks to every 8 weeks). Compared with HLA-C*06:02-POS patients, a modestly greater proportion of HLA-C*06:02-NEG patients experienced an adjustment in dosing interval (every 12 weeks to every 8 weeks) (49.5% vs. 42.6%; Table 3), or an adjustment in dosing interval and dose (45 to 90 mg) (41.4% vs. 32.6%; Table 3). Consistent with this pattern, a slightly larger proportion of HLA-C*06:02-POS patients (57.5%) did not receive any adjustment in dosing interval or dose compared with HLA-C*06:02-NEG (50.5%) patients (Table 3).

DISCUSSION

Through genome-wide association studies, greater than 40 susceptibility loci for psoriasis have been identified, including polymorphisms in genes associated with innate and adaptive immunity (*TRAF3IP2*, *IL-23R*, *IL-12B*, *ERAP1*, *STAT3*, and *TYK2*, among others) (Nair et al., 2009; Strange et al., 2010; Sun et al., 2010; Tsoi et al., 2015). Genetic variations in these genes highlight the importance of antigen presentation, the IL-12/23 axis, and T cells in psoriasis, but polymorphisms in some of these genes have been correlated with response to biological treatments. For example, two single-nucleotide polymorphisms in the gene encoding *TNFAIP3* have been correlated with response to TNF blockers (Tejasvi et al., 2012). Recently, the utility of HLA-C*06:02 as a pharmacogenetic marker of treatment response to ustekinumab, an IL-12/IL-23p40 inhibitor, has been explored (Talamonti et al., 2016).



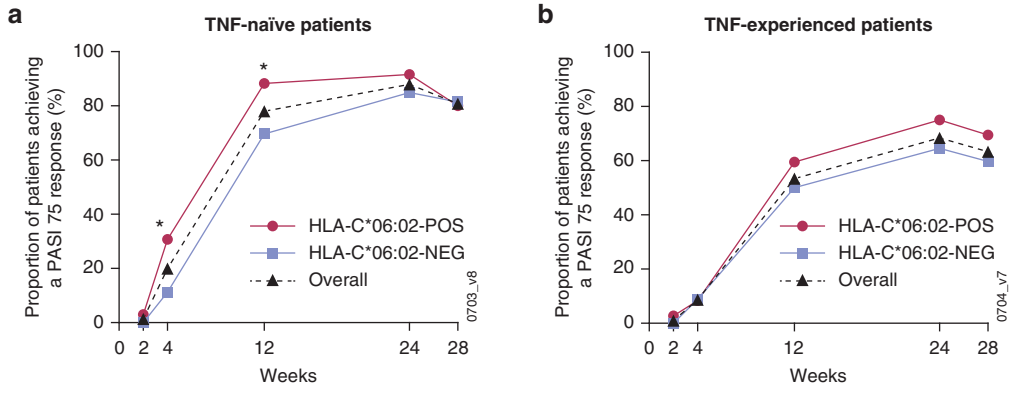
Week	2	4	12	24	28
N	110	110	110	95	95
HLA-C*06:02-POS	2.27	25.00	84.09	86.84	71.05
HLA-C*06:02-NEG	0.00	15.15	62.12	77.19	75.44
Overall	0.91	19.09	70.91	81.05	73.68
δ POS vs. NEG	2.30	9.80	22.00	9.60	-4.30
δ POS vs. Overall	1.30	5.90	13.10	5.70	-2.60

Week	2	4	12	24	28
N	58	58	58	37	37
HLA-C*06:02-POS	0.00	19.05	76.19	92.86	71.43
HLA-C*06:02-NEG	0.00	2.70	51.35	69.57	65.22
Overall	0.00	8.62	60.34	78.38	67.57
δ POS vs. NEG	0.00	16.40	24.80	23.30	6.20
δ POS vs. Overall	0.00	10.50	15.90	14.50	3.80

Figure 2. Psoriasis Area and Severity Index (PASI) response by weight-based dosing. The proportion of human leukocyte antigen (HLA)-C*06:02-positive (POS) and -negative (NEG) patients achieving a 75% improvement in PASI from baseline (PASI 75) based on weight-based dosing. (**a**) Patients weighing <100 kg received ustekinumab 45 mg and (**b**) patients weighing ≥100 kg received ustekinumab 90 mg. δ, difference between values.

In our study, the association of the HLA-C*06:02 with response to ustekinumab was confirmed and further explored in a relatively large cohort of well-phenotyped patients with moderate-to-severe psoriasis from three randomized placebo-controlled clinical trial populations (Griffiths et al., 2010; Leonardi et al., 2008; Papp et al., 2008). There was not a strong association with HLA-C*06:02 and maximal clinical response (PASI 90/PASI 100) to ustekinumab, and there was modest association with early clinical response (weeks 2—12) and good clinical response (PASI 75) that decreased over time. The logistic regression analysis evaluated 10 single nucleotide polymorphisms representing T helper type 17 pathway genes *IL-23R*, *IL-23A*, and *IL-12B* and found no significant association between any of these single nucleotide polymorphisms and PASI 75 or PASI 90 response to ustekinumab. Interactions of these genes and HLA-C*06:02 did not predict PASI 75 or PASI 90 responses to ustekinumab better than HLA-C*06:02 alone. Although the differences between HLA-C*06:02-POS and HLA-C*06:02-NEG patients was clearly discernable when comparing the overall population versus HLA-C*06:02-POS patients, the increase in efficacy for the HLA-C*06:02-POS population was minimal (approximately 10% or less). Therefore, the results from this retrospective study suggest that utilization of HLA-C*06:02 status for determining treatment may have limited clinical utility.

The prevalence of HLA-C*06:02 among North American patients sampled in this study, 41.9% (139 of 332) in ustekinumab-treated patients and 44.6% (233 of 532) in the overall cohort, is at the lower end of the reported range for white patients with psoriasis (42—66.9%) (Enerbäck et al., 1997; Gudjonsson et al., 2002; O'Brien et al., 2001; Tiilikainen et al., 1980). There is a potential bias in retrospective studies by unbalanced participation of patients with a positive clinical trial experience. Of the patients who were approached to provide DNA samples for this retrospective analysis, the overall participation rate was high, approximately 80%. In addition, the clinical response rates of the



Week	2	4	12	24	28
N	226	226	227	157	156
HLA-C*06:02-POS	2.97	30.69	88.24	91.55	80.00
HLA-C*06:02-NEG	0.00	11.20	69.60	84.88	81.40
Overall	1.33	19.91	77.97	87.90	80.77
δ POS vs. NEG	2.97	19.49	18.64	6.67	-1.40
δ POS vs. Overall	1.64	10.78	10.27	3.65	-0.77

Week	2	4	12	24	28
N	105	104	105	98	98
HLA-C*06:02-POS	2.70	8.33	59.46	75.00	69.44
HLA-C*06:02-NEG	0.00	8.82	50.00	64.52	59.68
Overall	0.95	8.65	53.33	68.37	63.27
δ POS vs. NEG	2.70	-0.49	9.46	10.48	9.76
δ POS vs. Overall	1.75	-0.32	6.13	6.63	6.17

Figure 3. Psoriasis Area and Severity Index (PASI) response by tumor necrosis factor (TNF) status. The proportion of TNF-naïve (**a**) and TNF-experienced (**b**) patients achieving a 75% improvement in PASI from baseline (PASI 75) after ustekinumab treatment (45 and 90 mg dose groups combined). *$P < 0.05$ based on adjusted Fisher's exact test; δ, difference between values.

Table 2. Long-term efficacy in PHOENIX 1 patients receiving at least one dose of ustekinumab through 5 years

	HLA-C*06:02-POS patients (N = 69)	HLA-C*06:02-NEG patients (N = 87)	Total (N = 156)
PASI response, n (%)			
PASI 50	64 (92.8)[1,2]	70 (80.5)[1]	134 (85.9)
PASI 75	57 (82.6)[1,2]	56 (64.4)[1]	113 (72.4)
PASI 90	36 (52.2)[1]	36 (41.4)	72 (46.2)
PASI 100	18 (26.1)[1]	19 (21.8)	37 (23.7)
PGA score of 0 or 1	37 (53.6)[1]	39 (44.8)	76 (48.7)

Abbreviations: HLA, human leukocyte antigen; HLA-C*06:02-POS, HLA-C*06:02-positive; HLA-C*06:02-NEG, HLA-C*06:02-negative; PASI 50/75/90/100, at least a 50/75/90/100% improvement from baseline in Psoriasis Area and Severity Index (PASI); PGA, Physician's Global Assessment.
[1]HLA-C*06:02 status with higher response rate for a given endpoint.
[2]Fisher's exact test *P*-value < 0.05.

patients who provided DNA samples for this analysis are similar to the overall response rates for each clinical trial (PHOENIX 1, PHOENIX 2, and ACCEPT) when assessing the primary endpoint, indicating that despite the potential for selection bias, the patients included in this analysis are likely representative of the overall trial populations.

Methods to predict response to therapy are an important focus for immune-mediated diseases, as clinical manifestations of the disease may be similar across a population. However, the disease mechanisms could differ within a population, resulting in different responses in individual patients to the same therapy. Identifying patients who are more likely to respond or have a maximal response to a specific therapy or mechanism of action would be a significant advancement in the psoriasis treatment paradigm. However, efforts to identify predictors of response in immune-mediated diseases have been largely unsuccessful. When potential predictors have been discovered, the subsequent replication of results in independent cohorts of patients has not been pursued, or the replication has failed to demonstrate clinically relevant separation of responders and nonresponders to treatment (Ryan et al., 2011). This is likely due to immune diseases being driven by a combination of genetics and environmental factors, with no single factor acting as a primary driver. Psoriasis is unique in the family of immune-mediated diseases in that the clinical response to current biological therapies with related mechanisms of action is high (Nast et al., 2015). This differs from other immune-mediated diseases such as rheumatoid arthritis (Valesini et al., 2008) or inflammatory bowel disease (Peyrin-Biroulet and Lemann, 2011) in which, on average, fewer than 50% of patients achieve a good response and even fewer achieve a maximal response, such as remission. The high clinical response rates observed in patients with psoriasis points to a common mechanism driving disease in the majority of patients. Therefore, identifying a robust predictor of response that distinguishes true nonresponders or suboptimal responders remains a significant challenge, one that will likely require multiple factors and may not be limited to one genetic factor such as HLA-C*06:02. It is also unlikely that the predictor would be specific to a given therapeutic agent given the overlap in mechanisms of action among many of the current biologics (i.e., anti-IL-12p40, anti-IL-23p19, and anti-IL-17).

The association of the HLA-C*06:02 allele with response to ustekinumab has now been replicated in two independent cohorts; however, the magnitude of the level of efficacy achieved based on HLA-C*06:02 status has varied (Chiu et al., 2014; Talamonti et al., 2013). One study that evaluated 51 patients with psoriasis reported that 96.4% of HLA-C*06:02-POS patients achieved a PASI 75 response at week 12, compared with 65.2% of HLA-C*06:02-NEG patients (Talamonti et al., 2013). A difference was also noted for the higher response rate of PASI 90, with 85.7% of HLA-C*06:02-POS patients achieving PASI 90 at week 12 compared with 56.5% of HLA-C*06:02-NEG patients (Talamonti et al., 2013). Another study of a Chinese population with a lower incidence of HLA-C*06:02-POS patients (8 of 66; 12%) reported that 75% of HLA-C*06:02-POS patients achieved a PASI 75 response compared with 45% of HLA-C*06:02-NEG-patients after 16 weeks of ustekinumab treatment (Chiu et al., 2014). The reasons for variability in reported rates may be attributed to several factors that differed between the

Table 3. Proportion of patients from the PHOENIX 2 study who experienced dose (ustekinumab 45 to 90 mg) and dosing interval (every 12 weeks to every 8 weeks) adjustment by HLA-C*06:02 status

	HLA-C*06:02-POS patients	HLA-C*06:02-NEG patients	*P*-value[1]
Adjustment in dosing interval (ustekinumab q12w to q8w)			
N	94	107	
n (%)	40 (42.6)	53 (49.5)	0.3951
Adjustment in dosing interval (q12w to q8w) and dose (45 to 90 mg)			
N	43	58	
n (%)	14 (32.6)	24 (41.4)	0.1883
No adjustment in dosing interval or dose			
N	94	107	
n (%)	54 (57.5)	54 (50.5)	–

Abbreviations: HLA, human leukocyte antigen; HLA-C*06:02-POS, HLA-C*06:02-positive; HLA-C*06:02-NEG, HLA-C*06:02-negative; q8w, every 8 weeks; q12w, every 12 weeks.
[1]Based on Fisher's exact test between groups with vs. without dose/dosing interval adjustment.

independent cohorts, including sample size, prevalence of HLA-C*06:02, early onset psoriasis, sex, and baseline disease severity. One key factor may be that the small studies were open-label (Talamonti et al., 2013) with patients exhibiting higher PASI 75 responses rates at week 12 (80.8%) than the patients in the current analysis from the randomized, placebo-controlled studies from the phase 3 ustekinumab clinical trials (70.2%). A recently published retrospective study assessing long-term outcomes reported that 18% more HLA-C*06:02-POS patients than HLA-C*06:02-NEG patients achieved at least a PASI 75 response at 3 years (Talamonti et al., 2016). These results are comparable with our findings in which 18.2% more HLA-C*06:02-POS patients than in the HLA-C*06:02-NEG population achieved a PASI 75 response at 5 years.

The push toward personalized medicine in patients with psoriasis and other immune-mediated diseases will benefit from the use of large, independent cohorts of well-characterized patients with objective measures of response and sufficient exposure to therapy to identify predictors of response in these complex heterogeneous diseases. The results of this study establish that patients with moderate-to-severe psoriasis who have the HLA-C*06:02 allele exhibit a modest increase in likelihood of response to ustekinumab, especially at early time points and lower response thresholds compared with patients who do not. The biological rationale for this is unknown and may be related to HLA-C*06:02 and/or other unknown factors. Practically, the modest difference in response between HLA-C*06:02-POS patients and HLA-C*06:02-NEG patients over longer periods of time and at the increasingly relevant, higher response thresholds does not provide a clear rationale for using HLA-C*06:02 genotyping for directing the choice of therapy.

MATERIAL AND METHODS

Patients

North American study participants randomized and treated in at least one of the following ustekinumab psoriasis phase 3 studies, PHOENIX 1 (Leonardi et al., 2008), PHOENIX 2 (Papp et al., 2008), and ACCEPT (Griffiths et al., 2010), were approached for permission and the retrospective collection of DNA samples. Every patient who agreed to participate in the retrospective study provided two buccal swab samples for DNA and Institutional Review Board-approved written informed consent. Overall, samples were obtained from a total of 601 patients. Of the 601 patients, 523 of European descent were used to assess the association between HLA-C*06:02 status and psoriasis characteristics, and 332 patients of European descent who had been randomized to receive ustekinumab treatment at baseline in their respective trials were assessed for the HLA-C*06:02 association with ustekinumab response.

PHOENIX 1 (Leonardi et al., 2008) and PHOENIX 2 (Papp et al., 2008) are randomized placebo-controlled studies in which patients with moderate-to-severe psoriasis received ustekinumab for up to 5 years (Langley et al., 2015; Papp et al., 2013). The ACCEPT study (Griffiths et al., 2010) compared the efficacy and safety of ustekinumab versus etanercept for the treatment of moderate-to-severe plaque psoriasis for up to 44 weeks of treatment. From PHOENIX 1 and PHOENIX 2, only patients who received ustekinumab 45 or 90 mg at week 0 were included in the analysis, excluding placebo-treated patients who crossed over to receive ustekinumab at week 12. For the ACCEPT study, only data from ustekinumab-treated patients in the active comparator-controlled portion (through week 12) were included in this report.

Patients from PHOENIX 1 who received at least one dose of ustekinumab were used to evaluate the association between HLA-C*06:02 status and long-term efficacy, up to week 244. PHOENIX 2 data were used to evaluate HLA-C*06:02 status and the need for dose escalation.

DNA extraction and genotyping

DNA extraction was completed using a buccal swab isolation kit (IsoHelix, Harrietsham, Kent, UK). DNA quality and integrity was checked before applying to genotyping processing. Samples were genotyped by two independent methods: (i) the HumanOmni2.5-8 (Omni2.5) BeadChip from Illumina (San Diego, CA) in accordance with the manufacturer's instructions. The Omni2.5 chip features approximately 2.5 million markers that capture variants down to minor allele frequency of 2.5% across diverse human populations; (ii) sequence-specific primer polymerase chain reaction as described previously (Talamonti et al., 2013). DNA extraction and genotyping were performed by Expression Analysis (Durham, NC). Both imputation and the sequence specific PCR methods were utilized to determine HLA-C*06:02 status, and the two methods are more than 95% concordant (Supplementary Table S2 online). Therefore, only the data utilizing the imputation method are presented.

HLA imputation

The SNP2HLA software package (http://www.broadinstitute.org/mpg/snp2hla/) was used to impute the HLA-C genotypes from the Omni2.5 chip data. The allele counts were dichotomized to Cw6-POS (patients with one or two copies of *06:02) or Cw6-NEG (patients with other HLA-C alleles). Note that this algorithm uses a panel of samples from white patients as a reference, and thus only 523 patients of European descent were included in this study (Jia et al., 2013). Principal component analysis was used to determine the genetic ancestry of the study patients.

Data analysis

Statistical analysis was conducted using ArrayStudio v9 (OmicSoft, Cary, NC). Similarity in patient demographics and psoriasis characteristics was assessed by the analysis of variance before clinical data from PHOENIX 1, PHOENIX 2, and ACCEPT were merged for analysis. Clinical data from all three trials were merged for assessments at weeks 2, 4, and 12, whereas only data from PHOENIX 1 and PHOENIX 2 were merged for assessments at weeks 24 and 28. Clinical responses to ustekinumab were analyzed and summarized by HLA-C*06:02 status (e.g., HLA-C*06:02-POS vs. HLA-C*06:02-NEG) over time. A two-tailed Fisher's exact test was conducted at each selected time point to compare the proportion of patients who achieved a clinical response to ustekinumab between patients with different genetic factor status. Benjamini-Hochberg false discovery rate was applied for multiple testing correction. Associations with Benjamini-Hochberg false discovery rate-adjusted P-values <0.05 were considered significant.

One-way analysis of variance was conducted to compare HLA-C*06:02-POS and -NEG patients in baseline psoriasis disease characteristics including age of onset, disease duration, and baseline PASI scores. Differences with P-value <0.05 were considered significant.

CONFLICT OF INTEREST

This study was funded by Janssen Research & Development, LLC. All authors are employees of Janssen Research & Development, LLC and own stock options in Johnson & Johnson, of which Janssen is a wholly-owned subsidiary.

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SUPPLEMENTARY MATERIAL

Supplementary material is linked to the online version of the paper at www.jidonline.org, and at http://dx.doi.org/10.1016/j.jid.2016.06.631.

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